Remarks

Favorable consideration of this application is respectfully requested in view of the foregoing amendment and the following remarks.

Claims 1-49 are pending in the application. Claims 1-49 have been rejected. Claims 1, 23, 35, and 47 have been amended. New claims 50-53 have been added, support for which can be found on page 15, line 13. No new matter has been added.

Objection to the Specification

The Examiner continues to dispute Applicants' use of "inverse," such as in "inverse labeling pattern," despite Applicants' having provided several definitions. As described on page 10, line 19, "The term 'inverse labeling pattern' means a qualitative mass shift or an isotope peak intensity ratio reversal, i.e., from the heavy-labeled signal being stronger to the light-labeled signal being stronger (or vice versa), detected between the two inverse labeled mixtures." Figure 1 provides an illustrative graphical representation of this method, in which both a "qualitative mass shift" (the example furthest to the left in both spectra, below the words "combine & analyze") and "an isotope peak intensity ratio reversal" (the examples 3rd and 5th from the left in both spectra, below the words "combine & analyze") can be seen. This method is further described throughout the present invention, including in the EXAMPLES section.

As Figure 1 and the remainder of the specification demonstrate- and as a person of ordinary skill in the art would easily recognize- an inverse relationship can be easily detected by non-quantitative means (e.g., visually) when making a comparison between labeling patterns in two sample mixtures in which:

- one sample mixture exhibits a pair of peaks of different heights; and
- the other sample mixture exhibits a pair of peaks of different heights that is inversely proportional to the first pair. Said inverse relationship can be either a "qualitative mass shift" or a "isotope peak intensity ratio reversal," as described below.

To use a hypothetical example supported by the present specification, if a person of ordinary skill in the art were to obtain labeling patterns from two sample mixtures by using the methods disclosed in the present application, and

- one sample mixture exhibits peaks of heights 2 and 4 for proteins A and B, respectively (on an arbitrary Y axis, for example, when graphically charted); and
- the other sample mixture exhibits peaks of heights 4 and 2 for proteins A and B, respectively (on the same arbitrary Y axis),
- an inverse labeling pattern is easily detected (in this case, a "isotope peak intensity ratio reversal").

Amending the above hypothetical example, still supported by the present specification, to:

- one sample mixture exhibits peaks of heights 2 and 0 for proteins A and B, respectively (on an arbitrary Y axis, for example, when graphically charted); and
- the other sample mixture exhibits peaks of heights 0 and 2 for proteins A and B, respectively (on the same arbitrary Y axis),
- the peaks will only appear as a single peak after subtractive comparison. Nevertheless, an inverse labeling pattern still exists, and is still easily detected (in this case, a "qualitative mass shift").

In view of the above, Applicants respectfully request this objection be withdrawn by the Examiner.

Rejection Under 35 USC §112, ¶ 2

Claims 1, 23, 35, and 47 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner has rejected the phrase "inverse labeling pattern."

With respect to the phrase "inverse labeling pattern" the Examiner states on page 3 of the outstanding Action:

> In claim 1, step(f), the recitation of "inverse labeling pattern" is indefinite because the scope of the definition of the term "inverse" is not clear in both Applicants' specification and Applicants' clarifying remarks. Applicants argue that the term "inverse labeling pattern" is broadly defined on page 11 of the specification meaning "a qualitative mass shift or an isotope peak intensity ratio reversal" (See Applicants' Reply at p.4, second paragraph, lines 2-4) (emphasis added). However, Applicants also acknowledge that the term " inverse" has a more limited definition meaning "a reversal in the signal intensity ratio" (see Applicants' Reply at sentence bridging pp. 4-5). Both Applicants' specification and Applicants' clarifying remarks do not appear to resolve how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse", dictionary or otherwise, applies to the concept of a qualitative mass shift."

Without acquiescing to the Examiner's rejection, Applicants have amended claims 1, 23, 25, and 47, to omit the phrase "inverse labeling pattern," thereby obviating the rejection with respect to those claims (and with respect to the remainder of claims 1-49 depending therefrom). Withdrawal of the rejection of Claims 1, 23, 25, and 47 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection Under 35 USC §102(e)

Claims 1-12, 14, 16-19, 21-22 and 47-49 have been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,391,649 (Chait et al.). In particular, the Examiner stated:

> "Chait et al. describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2^{+}'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2^{-}'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of CLN2^{+} plus 1 mL of ^{15}N-labeled extract of clin2^{-}"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of cln2^{-} plus 1 mL of ^{15}N-labeled extract of CLN2^{+}"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1.-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV)."

Applicants traverse this rejection and respectfully submit that Claims 1-12, 14, 16-19, 21-22 and 47-49 are not anticipated by Chait et al.

Beginning with the above-cited paragraph, Applicants believe the Examiner has incorrectly matched portions of the Chait reference to elements of the claims of the present invention, in his attempt to demonstrate that all elements of the claims are anticipated by Chait et al. By way of non-limiting example, **step e** of independent claim 1 ("detecting the labeled proteins from each of the two mixtures")(**step d** of independent claim 47) of the present application is not anticipated by Chait et al. Chait clearly requires the isolation of individual proteins (from the mixture in which the cell pools containing the protein were combined) before

mass spectroscopy analysis is performed, whereas the detection or analysis of independent claim 1 is performed on the mixtures themselves.

Chait et al. isolate at least one protein from the mixture in order to minimize the complexity of the spectrometric scan, and to calculate peak intensity ratio for each peptide. This isolation step is seen as early as the abstract in the Chait et al. reference, for example: "The samples are combined and at least one protein is removed. The removed protein is subjected to mass spectroscopy to develop mass spectrum." In Figure 3, step 40, of Chait et al., the proteins are separated before any analysis is conducted. Likewise at column 3, line 60 ("...and at least one protein is removed from the combined sample"). Likewise at column 6, lines 36 ("The mixture of proteins is then separated into the individual proteins or small groups of proteins, also by known techniques...").

This axiom is again seen in Chait et al., Example 2, oft-cited by the Examiner. In the example, Chait describes how the combined samples were separated by high performance liquid chromatography ("HPLC") and SDS-PAGE ***into several hundreds of proteins*** (column 13, line 25)(emphasis added) before any actual mass spectrometry analysis was performed.

Contrarily, **step e** of the present independent method claim 1 does not require any distillation, separation, extraction, etc. of the protein mixtures prior to detection or analysis. In fact, one of the ways in which the present invention improves upon the prior art is its ability to detect differential expression of proteins *within complex protein mixtures* (see, e.g., Figure 1). The ease of detection of differentially expressed proteins, due to the inverse labeling pattern described in the present application, obviates a prerequisite separation or extraction step, and nicely qualifies the method to high-throughput experimentation.

By further way of non-limiting examples of the differences between Chait et al. and the presently claimed method, **step f** of independent claim 1 (**step e** of independent claim 47) is not anticipated by Chait et al. Amended step f reads: "comparing the labeling pattern obtained for the labeled proteins in the first mixture with the labeling pattern obtained for the labeled proteins in the second mixture, wherein a qualitative mass shift or an isotope peak intensity ratio reversal between the two labeling patterns is indicative of a differentially expressed protein in the two different samples." Comparison step f entails identifying differentially expressed proteins from complex protein mixtures by noting relationships between two distinct labeling patterns derived therefrom: if the patterns exhibit a qualitative mass shift or an isotope peak intensity ratio reversal, than the protein is differentially expressed between the two original samples (e.g., from a normal and diseased subject); if the patterns do not exhibit a qualitative mass shift or an isotope peak intensity ratio reversal, the protein is not differentially expressed. As further discussed below, this determination is easily made without any quantitation, numerical ratio calculation, etc.

Further insight into step f may be found at page 15, line 13, of the present specification: "Accordingly with inverse labeling [*including qualitative mass shift and isotope peak intensity ratio reversal*], instead of quantitatively calculating the ratio of the isotopically light to isotopically heavy signals for every peptide as is carried out in prior art isotopic labeling methods for identifying the differentially expressed proteins, two data sets are readily compared to quickly identify peptides of such qualitative changes that are indicative of differentially expressed proteins" (emphasis added).

Still further insight into step f may be found beginning at page 19, line 5, of the present specification. Applicants describe in detail the problems associated with identifying differentially expressed proteins using conventional mass spectrometry (i.e., quantitative) approaches, as compared to the qualitative methods of the present invention. Before listing some of those problems, Applicants reiterate the qualitative nature of their approach (page 19, line 19): "In the application of the inverse labeling method, what one looks for is the qualitative mass shifts, not isotopic pattern, nor accurate mass shifts."

In direct contrast to step f of independent claim 1 of the present invention, Chait et al. requires a quantitative calculation by mass spectrometer. At page 3 of the present Office Action, the Examiner compares column 13, lines 14-15 of Example 2 of Chait ("Mass spectrum measurements were obtained") to step f of independent claim 1 of the present invention. With respect intended, this is an improper comparison, as the former is a quantitative measurement, and the latter qualitative- thus there is no anticipation of the claim.

As further proof, and as Applicants have previously stated, both of the experiments performed in Chait et al. Example 2 are not necessary, as they are in the in the case of the present claimed method. The Chait second experiment was carried out as part of the method validation, to rule out that any change in isotopic ratios was caused by the isotopic enrichment process itself. In this regard, the Examiner's attention is directed to Chait et al., col. 8, lines 61-67, which states

> "To ensure that the change in the ratios is not caused by the isotopic enrichment itself, the process of Fig 3 is preferably repeated with the other cell pool being isotopically enriched, i.e., if in the first run the treated cell pool is isotopically enriched, as in FIG 3, then in the second run, the control cell pool would be isotopically enriched."

Accordingly, the purpose of performing the second experiment in Example 2 was to rule out that isotope enrichment (growing cell in heavy medium) was a source of ratio change.

An optional second verification step (as in Chait) is quite different from a critical second experiment performed to gather data with which to make an essential comparison to a first set of data (as in the presently claimed method). For this reason, in addition to the above, independent claims 1 and 47, and therefore, dependent claims 2-12, 14, 16-19, 21-22, 48, and

49 are not anticipated by Chait et al. Applicants therefore respectfully request withdrawal of the rejection of Claims 1-12, 14, 16-19, 21-22 and 47-49 under 35 U.S.C. §102(e).

Rejection Under 35 USC §103(a)

Claims 23-28, 30, 32-40, 42 and 44-46 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Schnolzer et al., Electrophoresis, vol. 17, pp. 945-953 (1996) (Schnolzer et al.) in view of Chait et al. In particular, the Examiner stated:

> "Schnolzer et al. teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see p.950, col. 2, first full paragraph, line 2), proteolyzing each protein pool with isotopically labeled water (see p. 950, col.,2, first fully paragraph, line 3), combining the protein pools (see p. 950, col. 2, first full paragraph, line 2), detecting the labeled peptides (see p. 950, col. 2, first full paragraph, lines 15-17), and comparing the labeling pattern (see p. 950, col. 2, first full paragraph lines 6-8). Schnolzer et al. do not teach a method for identifying differentially expressed protein in two different protein samples."

The Examiner then reiterated his remarks regarding Chait et al. which were made to support the §102(e) rejection and concluded:

> "Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Schnolzer et al., to identifying differentially expressed protein in two different proteins samples because Chait et al. discovered a method for analyzing post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g., drugs, hormones, etc.) in two or more biological samples (see col.3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col.1, lines 28-54). In addition, Chait et al., discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).
> With respect to claim 35, step (c), Schnolzer et al. teach a method wherein "peptide products continue to interact with these proteases and undergo repeated binding/hydrolysis cycles, resulting in complete equilibrium of both oxygens in the carboxy terminus of the fragment with oxygen from solvent water" (see Abstract)."

Applicants respectfully traverse this rejection. In view of the above-stated arguments (in opposition to the §102(e) rejection), Applicants are of the belief that Chait et al. does not anticipate each and every element of claims 1-12, 14, 16-19, 21-22 and 47-49 under 35 U.S.C. §102(e). Therefore, Applicants are of the belief that an obviousness rejection of related claims 23-28, 30, 32-40, 42 and 44-46 is improper in view of combined references that include Chait et al. Nevertheless, without acquiescing to the Examiner's stated position, Applicants offer the following in support of a non-obvious verdict of Claims 23-28, 30, 32-40, 42 and 44-46:

Schnolzer et al. is directed to a method of digesting proteins in enriched $H_2{}^{18}O$ for use in identifying proteins. While Schnolzer et al. indicate on p. 950, second full paragraph, that a protein sample is divided into two equal parts, and the parts are combined, Schnolzer et al. do not teach or specifically suggest a method for identifying differentially expressed proteins by performing a second experiment with a different protein sample which is also divided into two equal parts and combined, and wherein the label in the first experiment is reversed from the second experiment as set forth in steps (a-d) of Claim 23. Further, Schnolzer et al. do not teach or specifically suggest comparing the labeling pattern obtained for the labeled peptides in the first and second experiments (i.e., protein mixture in present claim 23), wherein an inverse labeling pattern of a peptide detected between the first and second experiments, is indicative of the differentially expressed protein from which the peptide originated.

As stated above in addressing the §102(e) rejection, Chait et al. fail to teach or specifically suggest comparing the labeling patterns obtained from the two experiments, nor does Chait et al. indicate that an inverse labeling pattern, a reversal in the signal intensity ratio of the isotopic pairs of a peptide between the first experiment and the second experiment, is indicative of a differentially expressed protein from which the peptide originated. Thus, Schnolzer et al. fail to remedy the deficiency present in Chait et al. Accordingly, the combination of Schnolzer et al. and Chait et al. does not make obvious Claims 23-28, 30, 32-40, 42 and 44-46.

In view of the above, withdrawal of the rejection of Claims 23-28, 30, 32-40, 42 and 44-46 under 35 U.S.C. §103(a) is respectfully requested.

Claims 13, 15 and 20 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,670,194 (Aebersold et al.) in view of Chait et al. In particular, the Examiner stated:

> "Aebersold et al. teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see col. 5, lines 61-66), labeling each protein pool with an isotopically different labeling reagent (see col. 5, lines 61-66), combining the protein pools (see col. 6, lines 2-3), detecting the labeled peptides (see col. 6, line 9), and comparing the labeling pattern (see col. 6, line 13). With respect to claims 13 and 15, Aebersold et al. teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a). With respect to claim 20, Aebersold et al. describe a labeling reagent containing an affinity tag (see Abstract)."
> "Aebersold et al. do not provide two protein pools from each of a reference and an experimental sample."

With respect to Chait et al., the Examiner reiterated his assertions made in the §102(e) rejection and then stated:

> "Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Aebersold et al., by providing two protein pools from each of a reference and an experimental sample because Chait et al. discovered that differentially expressed proteins can be analyzed for post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g. drugs, hormones, etc.) on two or more biological samples (see col. 3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). In addition, Chait et al. discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64)."

Applicants traverse this rejection and respectfully submit that the combination of Aebersold et al. and Chait et al. does not make obvious Claims 13, 15 and 20 for the reasons stated below.

Aebersold et al. is directed to a method for quantitating proteins in one or more biological samples containing protein mixtures utilizing chemically identical, affinity tagged and differentially isotopically labeled reagents. In particular, Aebersold et al. teach the steps of providing a protein pool from two different samples, labeling the protein pools with an isotopically different labeling agent, combining the two labeled pools, enzymatically digesting the proteins to generate peptides, and detecting the labeled peptides. Aebersold et al., however, do not teach or specifically suggest comparing the labeling patterns obtained from the two different pools as is asserted by the Examiner. Instead, Aebersold et al. indicate in col. 6, lines 12-15 that "The relative amounts of a given protein in each sample is determined by comparing relative abundance of the ions generated from any differentially labeled peptides originating from the protein." Accordingly, from the one experiment involving two protein pools labeled with a differentially isotopically labeled agent, Aebersold et al., as is the case in Chait et al., would have to calculate the isotopic peak intensity ratio (between the light isotope labeled peak and the heavy isotope labeled peak) for each peptide. The only way Aebersold would be able to show that there was a differentially expressed protein, i.e., a protein whose abundance differed in a significant manner from the other proteins was to compare the intensity ratios (calculated from the isotopic pair obtained for each peptide) of all the peptides in the one experiment to identify the differentially expressed proteins. As acknowledged by the Examiner, Aebersold et al. does not teach or specifically suggest providing two protein pools from each of a reference and an experimental sample. No where does Aebersold et al. indicate that the labeling pattern of the combined pools from the first experiment is compared to the labeling pattern of the combined pools from the second experiment (wherein the labeling was reversed), and that an inverse labeling pattern of a protein detected between the first and second

experiments is indicative of a differentially expressed protein as recited in step (f) of amended independent Claim 1.

With respect to Chait et al., Applicants reiterate the arguments proffered to address the §102(e) rejection, namely that Chait et al. does not teach or specifically suggest comparing the labeling patterns obtained from the two experiments, nor does Chait et al. teach or specifically suggest that an inverse labeling pattern, a reversal in the signal intensity ratio of the isotopic pairs of a protein between the first experiment and the second experiment, is indicative of a differentially expressed protein as defined in step (f) of independent Claim 1. Thus, Aebersold et al. fail to remedy the deficiency present in Chait et al.

It is further noted that as acknowledged by the Examiner, the second experiment in Chait et al. was performed to ensure that any change in isotopic ratios was not caused by the isotopic enrichment itself (see, e.g., the outstanding Action page 8, lines 1-2). In contrast, one skilled in the art utilizing the chemical labeling as described in Aebersold et al., would not perform a second experiment, as was done in Chait et al., to confirm the isotopic ratios in the first experiment, since it would not be expected that isotopic labeling utilizing Aebersold's chemically identical protein labeling reagent would change the isotopic ratios. Accordingly, one skilled in the art armed with the knowledge of Aebersold's chemical labeling method would not be motivated to utilize the Chait et al. method to perform a second experiment to confirm the results from the first experiment.

Accordingly, in view that 1) neither Aebersold et al. nor Chait et al. teach or specifically suggest comparing the labeling patterns obtained from two experiments as is set forth in step (f) of Claim 1, 2) nor do these references teach or specifically suggest that an inverse labeling pattern, a reversal in the signal intensity ratio of the isotopic pairs of a protein between the first experiment and the second experiment, is indicative of a differentially expressed protein, and 3) that one skilled in the art would not be motivated to combine Aebersold et al. with Chait et al., specifically Example 2, the combination of Aebersold et al. and Chait et al. does not make obvious Claims 13, 15 and 20 which depend from amended independent Claim 1.

In view of the above, withdrawal of the rejection of Claims 13, 15 and 20 under 35 U.S.C. §103(a) is respectfully requested.

Claims 29 and 31 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Schnulzer et al., Chait et al. as applied to Claim 23 and further in view of Aebersold et al. In particular, the Examiner stated:

> "Schnolzer et al. and Chait et al. describe a method for identifying a differentially expressed protein as substantially described supra.

> The aforementioned references do not teach a fractionation step prior to step (a)."
> However, Aebersold et al. teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a) as a preparative step in the analysis of membrane proteins (see col. 17, line 28). Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method of identifying differentially expressed proteins, as taught by Schnolzer et at. and Chait et al., with a fractionation step prior to step (a) because Aebersold et al. discovered that panning and labeling membrane proteins with isotopic affinity tags can be used to identify important diagnostic or therapeutic targets (see col. 17, lines 49-52) without the step of solubilizing membrane proteins prior to analysis, thus avoiding a major complication facing prior art methods which require solubilization of membrane proteins prior to analysis."

Applicants traverse this rejection and respectfully submit that the combination of Schnolzer et al., Chait et al., and Aebersold et al. does not make obvious Claims 29 and 31.

The same arguments proffered above to address the §102(e) and §103(a) rejections apply equally to this rejection, namely that neither Schnolzer et al., Chait et al. or Aerbersold et al. each taken alone or combined teach or specifically suggest comparing the labeling patterns obtained from the two experiments, or that an inverse labeling pattern of a peptide detected between the first and second experiments is indicative of a differentially expressed protein from which the peptide originated as set forth in step (f) of amended independent Claim 23. Further, as discussed above with respect to the rejection of Claims 13, 15 and 20, one skilled in art would not be motivated to combine Aebersold et al. with Chait et al. Accordingly, the combination of Schnolzer et al., Chait et al. and Aebersold et al. does not make obvious Claims 29 and 31 which depend from Claim 23.

In view of the above, withdrawal of the rejection of Claims 29 and 31 under 35 U.S.C. §103(a) is respectfully requested.

Claims 41-43 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Schnolzer et al., Chait et al. as applied to Claim 35 and further in view of Aebersold et al. In making this rejection the Examiner reiterated the same remarks regarding Schnolzer et al., Chait et al. and Aebersold et al. as were made in the rejection of Claims 29 and 31 under 35 U.S.C. §103(a).

Applicants traverse this rejection and respectfully submit that the combination of Schnolzer et al., Chait et al. and Aebersold et al. does not make obvious Claims 41-43.

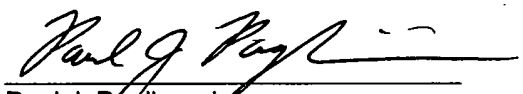
The same arguments proffered above to address the §102(e) and §103(a) rejections apply equally to the rejection of Claims 41-43, namely that neither Schnolzer

et al., Chait et al. or Aerbersold et al. each taken alone or combined teach or specifically suggest comparing the labeling patterns obtained from the two experiments wherein the label was reversed in the two experiments, or that and that an inverse labeling pattern of a peptide detected between the first and second experiments is indicative of a differentially expressed protein from which the peptide originated as set forth in step (g) of amended independent Claim 35. Further, as discussed above with respect to the rejection of Claims 13, 15 and 20, one skilled in art would not be motivated to combine Aebersold et al. with Chait et al. Accordingly, the combination of Schnolzer et al., Chait et al. and Aebersold et al. does not make obvious Claims 41-43 which depend from Claim 35.

In view of the above, withdrawal of the rejection of Claims 41-43 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below.

Respectfully submitted,



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